GPCR HETEROMER INHIBITORS AND USES THEREOF

CROSS REFERENCE

[0001] This application claims the benefit of priority from U.S. Provisional Application No. 62/607,876, filed Dec. 19, 2017, and further claims the benefit of priority from U.S. Provisional Application No. 62/679,598, filed Jun. 1, 2018, and further claims the benefit of priority from U.S. Provisional Application No. 62/732,946, filed Sep. 18, 2018. Each of the foregoing related applications, in their entirety, are incorporated herein by reference.

[0002] In addition, each of the references identified herein, in their entirety, are incorporated herein by reference.

SEQUENCE LISTING

[0003] This application incorporates by reference in its entirety the Computer Readable Form (CRF) of a Sequence Listing in ASCII text format submitted via EFS-Web. The Sequence Listing text file submitted via EFS-Web, entitled 14462-009-999_SEQ_LISTING.txt, was created on Dec. 17, 2018, and is 3,018 bytes in size.

BACKGROUND OF THE INVENTION

[0004] The invention disclosed herein relates generally to inhibitors of novel, functional GPCR heteromers, and more specifically to inhibitors of CXC receptor 4 (CXCR4)-G protein-coupled receptor (GPCR) heteromers that display enhanced signaling downstream of CXCR4 as a result of functional heteromer formation and that are associated with cancers and other diseases.

[0005] G protein-coupled receptors (GPCRs) are seven-transmembrane domain cell surface receptors that are coupled to G proteins. GPCRs mediate diverse sensory and physiological responses by perceiving stimuli including light, odorants, hormones, neurotransmitters, chemokines, small lipid molecules, and nucleotides. There are approximately 800 GPCR genes in human genome, and more than half of them are predicted to encode sensory receptors such as olfactory, visual, and taste receptors (Bjarnadottir, et al., 2006). The remaining 350 GPCRs have physiologically important roles in embryonic development, behavior, mood, cognition, regulation of blood pressure, heart rate, and digestive processes, regulation of immune system and inflammation, maintenance of homeostasis, and growth and metastasis of cancers (Filmore 2004, Overington, et al., 2006). GPCRs are associated with many diseases and are the targets of approximately 40% of all prescription drugs (Filmore 2004).

[0006] CXC receptor 4 (CXCR4) is a member of the chemokine receptor family GPCR. CXCR4 is expressed on most of the hematopoietic cell types, bone marrow stem cells, endothelial progenitor cells, vascular endothelial cells, neurons and neuronal stem cells, microglia and astrocytes (Klein and Rubin 2004, Griffith, et al., 2014). CXCR4 responds to its ligand C-X-C Motif Chemokine ligand 12 (CXCL12), also known as Stromal cell-derived factor 1 (SDF-1), and has essential roles in the embryonic development of the hematopoietic, cardiovascular, and nervous systems (Griffith, et al., 2014). CXCR4 was discovered as a co-receptor for human immunodeficiency virus (HIV), and has important roles in the homing of hematopoietic stem cells (HSCs) to the bone marrow, inflammation, immune surveillance of tissues, and tissue regeneration in adult (Chatterjee, et al. 2014). Mutations in the C-terminus of CXCR4 cause persistent CXCR4 activation, leading to a congenital immune deficiency called WHIM syndrome (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) characterized by neutropenia and B cell lymphopenia (Hernandez, et al., 2003; Kawai, 2009). CXCR4 also has essential roles in T and B lymphocyte development within lymphoid organs and the thymus during development and in adult (Allen, et al., 2004; Ara, et al., 2003).

[0007] CXCR4 is implicated in various immune and autoimmune diseases, such as HIV infection, ischaemia, wound healing, rheumatoid arthritis, systemic lupus erythematosus (SLE), interstitial pneumonias, vascular disease, multiple sclerosis, pulmonary fibrosis, and allergic airway disease (Chu et al., 2017; Debnath, et al., 2013; Domanska, et al., 2013). The involvement of CXCR4 in rheumatoid arthritis was demonstrated by the increased accumulation of CXCR4-positive T-cells in arthritic joints, and a reduction in collagen-induced arthritis in CXCR4-deficient mice (Buckley et al., 2000; Chung et al., 2010). Moreover, CXCR4 antagonist, AMD3100, alleviated collagen-induced arthritis significantly in a mouse model (De Klerck et al., 2005). CXCR4 also regulates pulmonary fibrosis by recruiting circulatory fibroblasts and bone marrow-derived progenitor cells during lung injury, and AMD3100 demonstrated a preventive effect in bleomycin-induced mouse pulmonary fibrosis (Song et al., 2010). CXCR4/CXCL12 axis is also implicated in the pathogenesis of SLE. In mouse models of lupus and patients with SLE, inflammatory cells such as monocytes, neutrophils, and B-cells showed increased expression of CXCR4 and migrated toward skin and lung that overexpress CXCL12 predominantly (Chong and Mohan, 2009; Wang et al., 2009; Wang et al., 2010). CXCR4 antagonist, CTCE-9908, prolonged survival and greatly improved disease conditions and nephritis in a mouse model of lupus (Wang et al., 2009). Furthermore, CXCR4 is also involved in brain and cardiac diseases including brain injury, stroke, myocardial infarction, atherosclerosis and injury-induced vascular restenosis (Cheng et al., 2017; Domanska, et al., 2013; Doring, et al., 2014).

[0008] The involvement of CXCR4 in cancer was first noticed when B cells from patients with chronic lymphocytic leukemia (B-CCL) express high levels of functional CXCR4 on the surface, showing enhanced calcium mobilization and actin polymerization upon CXCL12 exposure, and migration towards bone marrow stromal cells that secret CXCL12 (Burger, et al., 1999).

[0009] CXCR4 is subsequently characterized to be responsible for breast cancer metastasis to organs that express higher levels of CXCL12 such as lymph nodes, bone marrow, lung, and liver (Muller, et al., 2001). After initial discovery, increasing evidence indicates that CXCR4 is associated with a variety of different cancers and has multiple potential roles in malignancy. CXCR4 is overexpressed in more than 23 human cancers, including breast cancer, lung cancer, brain cancer, kidney cancer (or renal cell carcinoma), pancreatic cancer, ovarian cancer, prostate cancer, melanoma, leukemia, multiple myeloma, gastrointestinal cancers, and soft tissue sarcomas, and regarded as a poor prognosis marker (Domanska, et al., 2013; Chatterjee, et al., 2014; Furusato et al., 2010). CXCR4 is the only chemokine receptor that is expressed by the majority of cancer types